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| EXAMINER | |
|---|---|
| PORTNER, VIRGINIA ALLEN | |
| **ART UNIT** | **PAPER NUMBER** |
| 1645 | |

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33

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/252,691 | WEINSTOCK ET AL. | |
| | Examiner | Art Unit | |
| | Ginny Portner | 1645 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on *19 May 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☐ Claim(s) *1-9 and 29-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) *42* is/are allowed.

6)☐ Claim(s) *1-9,29-41 and 44-50* is/are rejected.

7)☐ Claim(s) *43* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. §§ 119 and 120**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

**DETAILED ACTION**

Claims 10-28 have been canceled.

Claims 1, 5,9, 29, 33, 37 and 50 have been amended.

Claims 1-9 and claims 29-50 are under consideration.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

***Response to Amendment***

2. Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn.

3. The Amendment After Final submitted April 28, 2003 has been entered.

***Allowable Subject Matter***

4. The isolated nucleic acid of claim 42 and the recombinant expression vector that comprises the--isolated-- nucleic of claim 42 that consists of SEQ ID NO 1394 define over the prior art of record.

***Rejections Withdrawn***

5. The rejection of claims 1-3,5-7,9, 29-31,33-36,38-40,43-44, 47-48, 50 under 35 U.S.C. 101 because the claimed invention is not supported by a specific, credible and substantial asserted utility or a well established utility for the elected invention of SEQ ID NO 7056 or SEQ ID No 1394 that encodes a polypeptide, is herein withdrawn in light of allowable subject matter having been indicated and new grounds of rejection set forth below.

6. The rejection of claims 1-3,5-7,9, 29-31,33-36,38-40,43-44, 47-48, 50 under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, credible and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention, is herein withdrawn in light of allowable subject matter having been indicated and new grounds of rejection set forth below.

7. The rejection of claims 5, 9, 29 (no specified size for the polypeptide) and 50 under 35 U.S.C. 102(b) as being anticipated by Blattner et al (January 29, 1997 (EMBL record, see sequence alignments **AE000213 and AAC74219**) or Oshima et al (1996,EMBL sequence alignments D90748 and BAA35957 ), is herein withdrawn in light of new grounds of rejection set forth below.

8. The rejection of claims 29, 33, 37-38 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid sequence SEQ ID No 1394 for the detection of E.cloacae in a sample, does not reasonably provide enablement for the use of any nucleic acid that only shares 70% sequence identity with SEQ ID No 1394, based upon nucleic acid changes encompassed by claiming the isolated nucleic acid sequence encoding SEQ ID No 7056. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use a nucleic acid sequence that only shares 70% sequence identity with SEQ ID 1394, the invention commensurate in scope with these claims, is herein withdrawn in light of new grounds of rejection set forth below.

***Rejections Maintained***

9. The rejection of claims 4,8,32,37,41,45,49 under 35 U.S.C. 101 because the claimed invention is not supported by a specific, credible and substantial asserted utility or a well established utility for the elected invention of SEQ ID NO 7056 or SEQ ID No 1394 that encodes a polypeptide, is maintained for reasons of record and in light of the fact that the polypeptide has not been defined to evidence any specific biological activity, has not been shown to function as a diagnostic antigen, or vaccine polypeptide or to be an E.cloacae specific reagent; the polypeptide has not been disclose to evidence either a specific, credible and substantial asserted utility or a well established utility.

10. The rejection of claims 4,8,32,37,41,45,49 under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, credible and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention, for reasons of record.

*New Grounds of Rejection*

*Claim Objections*

11. Claim 43 is objected to for minor informalities; the claim should recite the phase --isolated nucleic acid-- to set forth allowable subject matter.

12. Claims 2, 6,30,34,39,43,47 are objected to because of the following informalities: The claims should recite the phrase --isolated--nucleic acid to show that the vector is not a naturally occurring recombinant vector, so to show the hand of man. A vector that comprise the nucleic acid is not an isolated nucleic acid in the recombinant vector, and reads on the native nucleic acid, thus broadening the scope of the independent claim. The objection could be obviated through amending claims to recite the term ---isolated--. Appropriate correction is required.

13. Claim 35 is objected to because of the following informalities: Claim 35 recited the SEQ ID NO 1394 which is the entire nucleic acid sequence that encodes 7056; and depends from claim 33 that recites fragments of SEQ ID NO 7056. The isolated nucleic acid of claim 33 does not encode the entire SEQ ID NO 7056, based upon the recitation of specific ranges of amino acids that exclude the entire coding sequence of SEQ ID NO 1394. The cell of claim 35 would not express the polypeptide that SEQ ID NO 1394 encodes, in light of the fact that SEQ ID NO 1394 is larger than the nucleic acid sequence defined in claim 33 from which claim 35 depends. The full nucleic acid sequence SEQ ID NO 1394 and the complete polypeptide it encodes, SEQ ID NO 7056, lacks antecedent basis in claim 33 from which claim 35 depends. Appropriate correction is required.

*Claim Rejections - 35 U.S.C. § 112*

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 1-9, 29-41, 44-50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The following is a summary of the issues presented below:

I. Claims 1-4 recite the phase "encoding an E.cloacae polypeptide" and "comprises SEQ ID NO:1394".

II. Claims 5-8 directed to a genus nucleic acids (dependent claims directed to vectors, host cells and methods) that include fragments of SEQ ID NO 1394, specifically comprise least 25 sequential bases of SEQ ID NO 1394, and encode "an E.cloacae polypeptide".

III. Claims 9 and 50 are directed to a genus of probes that comprise fragments of SEQ ID NO 1394, specifically comprise least 25, or 30 sequential bases of SEQ ID NO 1394, respectively, but the genus is Not required to encode "an E.cloacae polypeptide".

IV. Claims 29-32 directed to a genus of nucleic acids (dependent claims directed to vectors, host cells and methods) that encode a polypeptide that comprises SEQ ID NO 7056.

V. Claims 37-41, directed to a genus of nucleic acids that encode a polypeptide, the polypeptide evidencing 90% or 95% sequence identity to the sequence SEQ ID NO 7056.

The specification defines the **nucleic acid sequence: SEQ ID NO 1394** to be:

* a sequence that starts with "gct" (a codon that encodes the amino acid "Ala"),

* a sequence of 669 nucleotides in length,

* the last three nucleic acids being "tga";

* the nucleic acid shares sequence homology with E.coli sequence "ymfc"; the E.coli nucleic acid sequence encoding a "hypothetical polypeptide" at the time of filing of the instant specification (definition provided in instant specification at page 178).

*the nucleic acid encodes an amino acid sequence of SEQ ID NO 7056 (see page 178, Table 2).

The specification defines the **amino acid sequence of SEQ ID NO 7056**:

* to be an E.cloacae polypeptide;

* not to evidence any specific biological function.

* nor any putative or hypothetical biological function through comparison to the E.coli hypothetical polypeptide of "ymfc". "ymfc" was defined by Blattner et al to encode a hypothetical peptide.

**Issue I,** Claims 1-4 are directed to nucleic acids that comprise SEQ ID NO 1394, and encode an E.cloacae polypeptide. SEQ ID NO 1394 is a sequence that does not start with "AUG", the first three nucleic acids not encoding "Met", a known start codon, designating the beginning of an open reading frame. SEQ ID NO 1394, based upon the sequences disclose, is only a partial open reading frame. No sequences that encode an E.cloacae polypeptide that comprises SEQ ID NO 1394 evidence original descriptive support in the instant specification. The specification does not provide original descriptive support for any other combinations of nucleic acids that encodes an E.cloacae polypeptide that comprise SEQ ID NO 1394. No isolated nucleic acids that comprise SEQ ID NO 1394 have been described in the instant specification that encode only an E.cloacae polypeptide. No nucleic acids that comprise SEQ ID NO 1394, and represent the entire open reading frame in which SEQ ID NO 1394 exists in nature, evidences original descriptive support.

Applicants have not described nor disclosed the "operon" which encodes the a gene. A functional bacterial gene encompasses much more than a protein coding region (see Davis et al., Microbiology, page 267). A bacterial gene is conventionally associated with positive and negative controlling elements such as promoters and regressors in a concordantly regulated transcription unit called an operon, without which, no protein is expressed. The specification fails to describe the functional gene *per se* (i.e., operon) and which applicants have intended to be encompassed by the comprising and encoding language of the instant claims as set forth *supra*. In a bacterial genome, the recitation of "comprising" SEQ ID NO:1394 or comprising a nucleic acid encoding SEQ ID NO:7056, includes regulatory sequences which are essential to the operation and

function of the structural gene in the operon. Moreover, the claims encompass and the specification contemplates and other open reading frames which are 3' and 5' to the polynucleotide sequence of SEQ ID NO:1394 and similarly encoding the amino acid sequence of SEQ ID NO:7056, such 5' and 3' information inclusive of the definition of an operon. These regulatory and other gene sequences of the operon that are not described, are essential to the function of a gene within the operon and are therefore essential elements. Such sequences fail to have an adequate written description in the instant specification. The specification does not provide written description support for any flanking nucleic acid sequences which are 5' or 3' of SEQ ID NO:1394 or that which comprise SEQ ID NO:7056. With the exception of an isolated polynucleotide consisting of SEQ ID NO: 1394 and an isolated polynucleotide consisting of a nucleotide sequence encoding SEQ ID NO:7056, the skilled artisan cannot envision all the contemplated nucleotide sequences by the detailed chemical structure of the claimed polynucleotides and therefore conception cannot be not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

**Issue II**:Claims 5-8 directed to a genus nucleic acids (dependent claims directed to vectors, host cells and methods) that include fragments of SEQ ID NO 1394, specifically comprise least 25 sequential bases of SEQ ID NO 1394, and encode "an E.cloacae polypeptide"

In addition to the issues addressed under Issue I above, Claims 5-8 raise an additional issue with respect to written descriptive support for a genus of nucleic acids that encode an E.cloacae polypeptide, of no specific biological function, of no specified size, and must only share 25 consecutive nucleic acids with SEQ ID No 1394.

What characteristics the claimed nucleic acid must have to insure the claimed nucleic acid to encode an E.cloacae polypeptide does not evidence original descriptive support.

Applicant asserts through submission of two references that the encoded polypeptides are pseudouridine synthases. It is the position of the examiner that the instant specification does not define any of the disclosed E.cloacae polypeptides to be pseudouridine synthases.

The first of the two references submitted by Applicant is Koonin (1996). Koonin discusses four families of enzymes with various amino acid sequence and sized polypeptides. None of the amino acid sequences are from E.cloacae, nor the "ymfc" sequence from E.coli.

"ymfc", is the only definition relative to an E.coli sequence provided in the instant specification. The claimed nucleic acid that encodes a E.cloacae polypeptide is not an enzyme from any of the sources as disclosed by Koonin et al. No original descriptive support for a polypeptide that is 325 amino acids in length (YFII,/Ecoli protein sequence P44445) and is encoded by a nucleic acid that comprises a sequence of 25 consecutive nucleic acids of SEQ ID No 1394 evidences original descriptive support.

Del Campo et al (2001) was cited for teaching "ymfc" to be a pseudouridine synthase in E.coli (see title, and page 1604, col. 2, paragraph 2). While it is true that Del Campo et al teach

"ymfc" to be a rluE open reading frame, Del Campo et al clearly provides evidence that the biological function of "ymfc" was not known at the time of filing of the instant specification by stating "In this work, we provide the evidence that the E.coli ORF ycil is rluB, ymfC is rluE". Therefore the polypeptide encoded by any 25 consecutive nucleic acids of SEQ ID No 1394, which appears to be an incomplete reading frame, was not taught to have any specific essential biological function as the biological function of "ymfc" was not known until October 2001; the effective filing date of the instant specification being February 1998, nor were E.cloacae functional variants of ymfc disclosed to reasonably convey that Applicant has possession of the claimed genus of nucleic acids at the time of filing.

**Issue III**: Claims 5 and 9 raise issues with respect to 35 U.S.C. 112, first paragraph (written description) similar to those addressed above under I and II above, but are not required to encode a polypeptide.

Claims 5 and 9 encompass polynucleotide sequences *comprising* SEQ ID NO:1394. None of these sequences meets the written description provision of 35 U.S.C. 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow

persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).

**Issue IV**: Claims 29-32 are directed to a nucleic acid that encodes a polypeptide which comprises SEQ ID NO 7056.

Upon reconsideration of the instant specification, no E.cloacae polypeptides that comprise SEQ ID NO 7056 were found to evidence original descriptive support. The encoded polypeptides of the claims that encode a polypeptide that comprise SEQ ID NO 7056. The instantly claimed invention does not require the polypeptide to evidence any specific biological function, no specific assays for retained function have been disclosed, no specific epitopes with a specified amino acid sequence essential for immunoreacting with a diagnostic E.cloacae antibody have been described; no diagnostic antibodies reactive with SEQ ID NO 7056 have been described; nor what kinds of changes that can be made to preserve E.cloacae character have been described when additional amino acids are added to the N-terminal or C-terminal of SEQ ID NO 7056.

The instant specification suggests a method of screening polypeptides encoded by a nucleic acid that differs from the disclosed nucleic acid, but a screen is not a method of making a nucleic acid that encodes a polypeptide; nor does a method of screening show possession of the genus of nucleic acids that encode a polypeptide that comprises SEQ ID No 7056 at the time of filing.

**Issue V**: Claims 37-41, directed to a genus of nucleic acids that encode a polypeptide, the polypeptide evidencing 90% or 95% sequence identity to the sequence SEQ ID NO 7056.

Issue V is similar to issue IV above, but may also comprise changes in SEQ ID NO 7056, within the internal amino acid sequence or is smaller than SEQ ID NO 7056. In so far as Issue V has been partially addressed under Issue IV, see above for embodiments that comprise SEQ ID NO 7056 and result in 90 % or 95 % sequence identity.

The claimed nucleic acid sequences encompass embodiments where the nucleic acids evidences the recited degree of change as compared to a reference nucleic acid sequence which encodes SEQ ID NO 7056; sequences that hybridize to the full complement of SEQ ID NO: 1394 and may or may not encode a polypeptide with any biological function, and may correspond to nucleic acid sequences from other bacterial species, mutated sequences, allelic variants. None of these sequences meets the written description provision of 35 U.S.C. 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).

A method of identifying a product does not show possession of the product at the time of filing. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC

1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. Similarly, applicants have not disclosed any information which is 3' and 5' to the polynucleotide sequence of SEQ ID NO:1394 and therefore clearly lacks written description for the broad class of polynucleotides comprising SEQ ID NO:1394. Thus, the written description of the instant specification does not provide for "comprising" language. In the instant case the specification provides only written description for a polynucleotide consisting of SEQ ID NO:1394 and a polynucleotide consisting of a nucleotide sequence encoding SEQ ID NO:7056.

The specification only discloses a polynucleotide sequence consisting of SEQ ID NO: 1394 which corresponds to the polynucleic acid sequence encoding the polypeptide SEQ ID No 7056. An isolated polynucleotide consisting of a nucleotide sequence encoding SEQ ID NO:7056, is also described by way of the written description in view of the art established principle of wobble variants of triplet codons for particular bacterial amino acids as described in basic textbooks. Thus, an isolated polynucleotide sequence consisting of SEQ ID NO: 1394 and an isolated polynucleotide consisting of a nucleotide sequence encoding SEQ ID NO:7056 meets the written description provision of 35 U.S.C. 112, first paragraph.

Therefore, only an isolated polynucleotide consisting of SEQ ID NO: 1394 and an isolated polynucleotide consisting of a nucleotide sequence encoding SEQ ID NO:7056, but not the full

breadth of the claim meets the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. (See page 1115.) Applicants are directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

16. Claims 33-36 and 46-49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 33-36 are directed to an isolated nucleic acid that encodes a polypeptide having the range of amino acids of 3-333, 6-333 or 13-222 of SEQ ID No 7056. Claims 33-36 define a subgenus of species that do not evidence original descriptive support. The claimed nucleic acids that comprise any one of the recited species have not been described. No specific guidance to select the recited ranges of encoded amino acids could be found to evidence original descriptive support in the instant specification. Therefore claims 33-36 recited New Matter.

Claims 46-49 are directed to an isolated nucleic acid consisting of nucleotides 7-669, 16-669 or 37-669 of SEQ ID NO 1394. The recited species of invention do not evidence original descriptive support and therefore define a genus of species that have not been described. While

species defined by the recitation of at least 25 consecutive nucleotides evidences original descriptive support, the exact species that recite a specific range of amino acids, set forth in the genus of nucleic acid molecules of claims 46-49, do not evidence original descriptive support. Claims 46-49 recite New Matter.

17. Claims 1-9 and claims 29-41, 43-50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling an isolated nucleic acid consisting of SEQ ID NO 1394, a vector and host that comprise SEQ ID NO 1394 or an isolated nucleic acid consisting of a sequence encoding SEQ ID No 7056 , does not reasonably provide enablement for nucleic acids that comprises SEQ ID NO 1394, comprises at least 25 or 30 consecutive nucleic acids of SEQ ID NO 1394, encode a polypeptide that shares a degree of variation relative to SEQ ID NO 7056 or SEQ ID NO 1394. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Scope of enablement Wands Factors:

a. the quantity of experimentation necessary: undue, in light of nucleic acids that encode therapeutic polypeptides is unpredictable in the art, and no showing of how or where the nucleic acid molecule can be changed or modified have been described. The nucleic acid is an incomplete open reading frame that does not start with "Met", and therefore the biological function of the encoded polypeptide is not known. While a nucleic acid with changes could be readily be made,

how the modified nucleic acid would function as a diagnostic agent or therapeutic have not been described, and the person of skill in the art would de novo, have to determine what changes would serve the asserted purpose of being a specific diagnostic reagent, or therapeutic the nucleic acid that encodes a polypeptide has not been defined to evidence any specific biological function, nor to be a target for biological agents used in therapy. Del Campo et al teaches knock-out mutants of what applicant asserts is the biological activity of the polypeptide, but the knock-out mutants grew just as well as the wild type strains, thus defining a non-essential gene, that would not serve as a target for therapeutic agents.

b. the amount of direction or guidance presented: none; undue as no specific guidance or teaching with respect to SEQ ID No 1394 or the nucleic acids that encode SEQ ID No 7056 are provided to produce a therapeutic polypeptide; or nucleic acids that comprise the recited portion, with or without a degree of change, or comprise the partial open reading frame; no assay provided to determine conserved function; no function defined for the encoded polypeptide; Also see Boslego and Ellis reference with respect to unpredictablity of vaccines that comprise a single polypeptide.

c. the presence or absence of working examples: no working example provided utilizing a nucleic acid comprising SEQ ID 1394 or the nucleic acid that encodes SEQ ID No 7056 as a vaccine, to screen for therapeutics, to react in an assay as a diagnostic.

d. the nature of the invention: Molecular biological techniques are well known in the art, but the utilization of variant nucleic acids, and small fragments to predictably detect a pathogen in

a mixed population of bacteria which share conserved sequences (E.coli and E.cloacae are both gram negative pathogens and share sequence homology and identity with the claimed invention, see Blattner et al sequence alignment previously provided), and presence of cross reactive epitopes would not serve to diagnose infection; and vaccines that comprise a single polypeptide are not predictable as therapeutic agents to prevent infection or to treat pre-established infection and disease (see Boslego et al, and Ellis et al; reference provided relative to the utilization of the nucleic acid to produce a polypeptide for therapeutic purposes)

e. the state of the prior art: high with respect to nucleic acids, moderate to high with respect to E.cloacae, and no previously identified pseudouridine synthatases for E.cloacae.

f. the relative skill of those in the art: high with respect to being able to produce synthetic or recombinant nucleic acids, and culturing cells.

g. the predictability or unpredictability of the art:

i. vaccines and therapeutics are unpredictable (see Boslego and Ellis; as well as Del Campo et al with respect to a pseudouridine synthase knock-out mutant that grew just as well as wild type cells (see Table 1, page 1610; reference provided by Applicant) ;

ii. absent specific guidance where changes in nucleic acid sequence would or could be tolerated so to predictably result in the production of a stable protein/polypeptides, that could be used in method of treating or diagnosing infection, one of skill in the art could not predict what the outcome would be when any type of change in reading frame were introduced into the nucleic acid; the nucleic acid being used in a method of making a polypeptide.

h.breadth of the claims: broad

18. Claims 1, 3,4,5,7,8, 35, 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the phrase "encoding an E.cloacae polypeptide, wherein the nucleic acid comprises SEQ ID NO 1394. No E.cloacae polypeptides have been described or defined that are encoded by a nucleic acid that comprises SEQ ID NO 1394. Only a polypeptide of SEQ ID NO 7056, which is encoded by SEQ ID NO 1394 has been defined, but no additional polypeptides encoded by a nucleic acid that is larger and comprises SEQ ID NO 1394 have been disclosed. Absent a specific definition of the invention, the nucleic acid that encodes a polypeptide larger than SEQ ID NO 7056, and comprises SEQ ID No 1394, is not distinctly claimed.

Claims 3, 7 recite the indefinite article "a". Which recombinant expression vector is present in the cell, if it is not --the-- recombinant expression vector ? Does the cell comprise the nucleic acid of the vector, or only the recombinant expression vector without the isolated nucleic acid?

Claims 4 and 8 are directed to a method of producing an E.cloacae polypeptide, the method comprising the step of culturing the cell. What is the polypeptide that is being produced and permitted to be expressed? Is the polypeptide being produced the polypeptide encoded by the transcription regulatory element or the isolated nucleic acid? E.cloacae excesses many types of polypeptides that are under the control of regulatory elements. What is the polypeptide being produced by the claimed method?

Claim 5 recites the phrase "An isolated nucleic acid encoded an E.cloacae polypeptide", "wherein the nucleic acid comprises at least 25 sequential bases of SEQ ID NO 1394." What are the 25 sequential bases of SEQ ID NO. 1394 that define a polypeptide sequence that is characteristic of E.cloacae? Twenty-five bases of SEQ ID NO 1394 would encode about 8 amino acids. What 8 amino acids that are encoded by SEQ ID NO 1394 that encode a polypeptide are characteristic only of E.cloacae ? In light of the definition of SEQ ID NO 1394 relative to an E.coli putative polypeptide that shares 85.6% identity at the amino acid level, the amino acid sequence alignment of the E.cloacae polypeptide not showing a sequence of 8 consecutive amino acids that are unique to E.cloacae at the polypeptide level, what is the claimed invention? (See sequence alignment provided at the polypeptide level, as the nucleic acid is claimed to encode a polypeptide). While claim 5 does not recite the amino acid sequence that SEQ ID NO 1394 encodes, the claim requires the claimed sequence to encode a polypeptide of E.cloacae, which is the amino acid sequence of SEQ ID NO 7056. The prior art shows that any polypeptide of 8 amino acids in length would not be an E.cloacae polypeptide, in light of the fact that "ymfc" of E.coli shares several regions of 8 amino acids or more, thus defining a polypeptide that is not a E.cloacae specific polypeptide. What genus of claimed nucleic acids are absent a specific definition is unclear.

Claims 4, 8,32,36,41,45 and 49 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: producing the E.cloacae polypeptide. The

preamble of the claimed method is directed to "A method of producing an E.cloacae polypeptide, and only recites the methods step of "culturing". How does the step of culturing correlate with the recited intended use of producing the polypeptide? Doesn't production of the polypeptide require expressing and isolating the polypeptide. The conditions are defined as being those that permit expression but the claimed method does not set forth the positive step of expressing and the encoded polypeptide, so to produce the polypeptide. The invention is not distinctly claimed.

Claims 35 and 36 recite SEQ ID NO 1394 which encodes the amino acid sequence of SEQ ID NO 7056 and depend from claim 33 which is directed to isolated nucleic acids that encode an amino acid sequence smaller than the entire amino acid sequence of SEQ ID NO 7056. The cell of claim 35 would not express the entire amino acid sequence encoded by SEQ ID NO 1394, as the entire sequence of 1394 is not encompassed by the claimed nucleic acids of claim 33. The method of claim 36 cultures the cell of claim 33 to permit the expression of the polypeptide encoded by SEQ ID NO 1394, but claim 33 is directed to isolated nucleic acids that are fragments of SEQ ID No 1394, evidencing ranges smaller than the entire polypeptide with all of the amino acids 7094; therefore the cell of that is cultured in the method of claim 36 would not express the entire sequence encoded by SEQ ID NO 1394 as only a portion of this sequence is encompassed by the nucleic acid of claim 33. A larger sequence recited in claims 35 and 36 depending from a claim that recites a smaller sequence, the dependent claims being directed to the a composition that can express or expresses the larger sequence is confusing. The invention is not distinctly claimed.

Claim 35 recites the phrase "the recombinant expression vector of claim 33"; claim 33 is directed to an isolated nucleic acid that is not defined to be recombinant, nor to be an expression vector; the phrase "recombinant expression vector" lacks antecedent basis in claim 33 from which it depends.

***Claim Rejections - 35 U.S.C. § 102***

19. Claims 3-4,7-8,31-32, 34-35, 40-41, 44-45, 48-49 are rejected under 35 U.S.C. 102(b) as being anticipated by Rattray et al (August 1995).

**Please Note**: The examiner is reading the phrase "cell comprising a recombinant expression vector" to include an E.cloacae cell that evidence changes from the wild type cell, but comprise all of the genes that normally are present in a E.cloacae cell.

(Cell compositions) Rattray et al discloses an E.cloacae recombinant vector cell (modified cell with lux plasmid (see page 2952, col. 1, paragraph 3) which inherently comprises the instantly claimed nucleic acid and is a recombinant expression vector comprising a transcription regulatory element (bacterial chromosomal DNA inherently comprises operons that include regulatory elements.

(method of culturing E.cloacae) Rattray et al also disclose a method of producing an E.cloacae polypeptide, the method comprising the step of :

culturing said cell to permit expression of the encoded polypeptides of the expression vector, the entire recombinant bacterial cell is a type of recombinant expression vector (see page 2951, Materials and methods, "preparation of microbial inocula").

The reference inherently anticipates the instantly claimed invention as the E.cloacae of the prior art was a recombinant expression vector that was cultured under conditions to permit expression of all the essential genes that provide for bacterial growth, to include the instantly claimed cell and method; the method not isolating any polypeptides, but only culturing the cell to permit expression of the E.cloacae polypeptides. Atlas Powder Co. V IRECA, 51 USPQ2d 1943, (FED Cir. 1999) states "Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art...However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. "The Court further held that "this same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art".

***Response to Arguments***

20. Rejections withdrawn will be addressed insofar as Applicant's traversal applies to the written description rejection set forth herein.

21. Applicant asserts that the claimed invention is adequately described, and the disclosed species of SEQ ID No 1394, which encodes SEQ ID NO 7056, provides adequate written descriptive support for the claimed genus.

22. It is the position of the examiner that analyses set forth in Example 9 of the Written Description Guidelines for a species to provide support for a genus claim are applicable to Applicant's claimed invention directed to isolated nucleic acids that encode a polypeptide.

a. The nucleic acid of Example 9 encodes a protein of a specific biological affinity for a receptor and stimulated a specific biological activity (enzymatic activity).

i.The instantly claimed nucleic acid is not disclosed to encode a polypeptide of any specific binding affinity, nor does the claimed nucleic acid encode a polypeptide of any specific biological activity, and does not stimulate any specific type of biological activity.

ii.No hybridization conditions are set forth in the claims to define a genus of nucleic acids that encode a polypeptide of any specific binding affinity or biological activity. No additional E.cloacae species of nucleic acid were identified as natural variants of the disclosed SEQ ID NO 7056. The nucleic acid of SEQ ID NO 1394 does not start with "Met", and therefore does not define the beginning of an open reading frame for a protein, the recited encoded polypeptide .

The instantly claimed invention does not meet the same or equivalent criteria set forth in Example 9 for a single disclosed species to be representative of a genus of nucleic acids that encode a protein of a specific function and contains a conserved essential chemical structure

relative to a reference sequence. Both characteristics are required by the example for the single disclosed species to provide sufficient enabling support for a genus claim.

The claimed invention encompasses substantial variation, for example the recitation of claim limitations "comprises at least 25 sequential bases of SEQ ID No 1394"; SEQ ID NO 1394 being a nucleic acid molecule of 669 nucleic acids, a combination of claim limitations defining a highly variant genus of nucleic acid molecules. Claims drawn to a nucleic acid that comprises SEQ ID NO 1394 also do not encode a polypeptide of any specific function, or binding affinity.

Applicant's analysis of the Written Description Guidelines does not correspond to the requirements, of structure correlated with function.

23. Applicant asserts that "functional domains for rsuA in other species were well known in the art".

24. It is the position of the examiner is that rsuA is not disclosed in the instant specification relative to SEQ ID NO 1394 or 7056. Table 2 discloses "ymfc" not rsuA. No biological function was defined for "ymfc", annotation in Table 2 to be a hypothetical protein of E.coli, not E.cloacae. Arguments directed to rsuA will not be further addresses, as original descriptive support for rsuA relative to the claimed invention was not disclosed, nor described.

25. The rejection of claims 4,8,32,37,41,45,49 under 35 U.S.C. 101 because the claimed invention is not supported by a specific, credible and substantial asserted utility or a well

established utility for the elected invention of SEQ ID NO 7056 or SEQ ID No 1394 that encodes a polypeptide, is maintained for reasons of record and in light of the fact that the polypeptide has not been defined to evidence any specific biological activity, has not been shown to function as a diagnostic antigen, or vaccine polypeptide or to be an E.cloacae specific reagent; the polypeptide has not been disclose to evidence either a specific, credible and substantial asserted utility or a well established utility.

The E.coli nucleic acid molecule "ymfc", at the time of filing the instant specification could have been interpreted to be a sequence starts with an internal methionine, or is a nucleic acid that should be read in a different reading frame (6 reading frames for each nucleic acid molecule, 3 from the 5' end, and 3 from the reverse 3' end of the molecule) or is a reading frame for a polypeptide the function of which is not known.

In so far as Del Campo et al is asserted to provide evidence for the claimed embodiments directed to a method of producing a polypetpide have utility for screening for therapeutics, it is the position of the examiner that Del Campo et al show at page 1610, Table 1, evidences that a knock-out mutant of the rluE gene (also known as "ymfc"), still grew with an equivalent doubling time to that of the wild type E.coli strain. No significant change in growth and replication time was evidenced in the "ymfc", also known as "rluE", thus defining the gene as non-essential to successful growth of the E.coli strain. Del Campo therefore provides evidence that rluE is not an essential gene for therapeutic purposes. Specific inhibition of rluE with a nucleic acid molecule

complementary to SEQ ID NO 1394, would not serve to inhibit bacterial growth, and therefore not function to inhibit or prevent bacterial infection or disease.

The specification asserts the disclosed nucleic acid to function as a therapeutic reagent; to "have utility to generate polypeptides(see page 39, lines 19-21)"; the polypeptides are asserted to function as vaccine polypeptides (see page 54, lines 10-25), as diagnostic reagents, and useful in screening for therapeutics (page 1, lines 14-18). Applicant proposes to identify therapeutics using the claimed nucleic acid that encodes a E.cloacae polypeptide. A polypeptide that does not evidence any specific biological activity, does not induce pathogen specific immunogenicity, or diagnostic capability would not be able to be used in methods of diagnosis and therapeutics; no nucleic acids differing in structure from SEQ ID NO 1394 have been described in light of no specific guidance or teaching has been provided as to where or how the claimed nucleic acid may be changed to ensure the polypeptide remains an E.cloacae polypeptide.

26. The rejection of claims 4,8,32,37,41,45,49 (methods of making a polypeptide of no specific biological function and not known to function as a therapeutic, diagnostic or vaccine polypeptide) under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, credible and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention, for reasons of record.

27. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first Friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

The Group and/or Art Unit location of your application in the PTO will be Group Art Unit 1645. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to this Art Unit.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vgp
January 12, 2004

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